FOLLOW UP OF TERM NEWBORN WITH HYPERBILIRUBINEMIA FOR ONE YEAR - FOR DEVELOPMENTAL AND AUDITORY ABNORMALITY

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CERTIFICATE

This is to certify that this dissertation entitled "**FOLLOW UP OF TERM NEWBORN WITH HYPERBILIRUBINEMIA FOR ONE YEAR - FOR DEVELOPMENTAL AND AUDITORY ABNORMALITY**" is a bonafide original work of **Dr.M.VINODH** in partial fulfillment of the requirement for **MD (Branch VII) Pediatrics** examination of the Tamil Nadu Dr.M.G.R Medical University to be held in April 2012

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DECLARATION

I, **Dr.M.VINODH**, solemnly declare that this dissertation **"FOLLOW UP OF TERM NEWBORN WITH HYPERBILIRUBINEMIA FOR ONE YEAR - FOR DEVELOPMENTAL AND AUDITORY ABNORMALITY"** is a bonafide record of work done by me in the Department of Pediatrics, Government Stanley Medical College and Hospital, Chennai under the guidance of **Prof. Dr. AMBIGAPATHY**, Director i/c, Institute of Social Pediatrics, Government Stanley Medical college and Hospital, Chennai-600101.

This dissertation is submitted to the **TamilnaduDr.M.G.R Medical University**, Chennai in partial fulfillment of the University Regulations for the award of MD degree (Pediatrics) **Branch- VII, Pediatrics** Examination to be held in April 2012.

Place: Chennai

Date: (**Dr.M.VINODH**)

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CONTENTS

INTRODUCTION

INTRODUCTION

Jaundice is the most common clinical sign in neonatal medicine, but rarely is it the harbinger of disease or associated with neurotoxicity. Some two-thirds of healthy term infants and almost all premature infants develop clinical jaundice in the first week of life[1]. Majority of this jaundice is physiological and results from an immature liver's excretory pathway for bilirubin at the time of its heightened production. In the current era of early postnatal discharge, jaundice is currently the most common reason for readmission to the hospital in the first week of life in western countries[2].

Concepts of bilirubin toxicity remain highly controversial. The problem is that bilirubin levels that are toxic to one infant may not be toxic to another, or even to same infant in different clinical circumstances. Currently, major debate surrounds the toxicity of bilirubin in otherwise healthy term infants and in premature, low birth weight infants[5].

Although all infants experience some degree of hyperbilirubinemia in the first few days of life and most have physiological jaundice, the extent and duration of the elevation vary among populations of different races in different geographic distributions[6].

This study was conducted to know the audiological and developmental outcomes of normal risk term newborns with serum total bilirubin of 20 mg/dl or more, who have had intervention for management of hyperbilirubinemia and had no neurological abnormality by clinical examination during their stay in the hospital.

REVIEW OF LITERATURE

REVIEW OF LITERATURE

Jaundice is the visible manifestation in the skin and sclera due to elevated serum concentration of bilirubin. Most adults are jaundiced when serum total bilirubin (STB) levels exceed 2.0mg/dl (34 micromol/dl). Neonates may not appear jaundiced until serum total bilirubin concentration exceeds 5mg/dl-7mg/dl[6]. Chemical hyperbilirubinemia defined as serum total bilirubin of 2mg/dl is virtually universal in newborns during first week of life. Serum total bilirubin concentration in premature infants is even higher, persists longer and are more likely to be associated with neurological injury than term infants.

Yellowish discoloration is first evident on the skin of the face, nasolabial fold and the tip of the nose. It is masked by the physiological plethora of the newborn and can be brought out by blanching the skin so that underlying yellowness of the subcutaneous tissues and blood vessels can be visualized. The jaundice must be looked for in good day light and there should be no yellow clothes or curtains in the background which can lead to an error of over estimation.

Neonatal jaundice is classified as physiological and pathological. This latter entity has been called nonphysiologic, although frequently no disease is identified as the cause.

CRITERIA THAT RULE OUT THE DIAGNOSIS OF PHYSIOLOGIC JAUNDICE[6]

1. Clinical jaundice in the first 24 hours of life.

2. Serum total bilirubin (STB) concentration increasing by more than 0.2mg/dl/hr or 5mg/dl/day.

3. Clinical jaundice persisting for more than 2 weeks in a full term infant.

4. Direct serum bilirubin concentration exceeding 1.5-2 mg/dl.

Physiologic jaundice can be divided into 2 phases[5]. Phase I includes the first 5 days of life in term infants and is characterized by rapid increase in STB levels for 3-4 days, after which the levels begin to decline. Phase II is characterized by stable, but elevated STB levels lasting for about 2 weeks. In contrast, in preterm infants, phase I lasts for 6-7 days, and STB levels reached are higher than those in term infants. After phase II, STB levels become comparable to adult levels.

The levels usually rise in full term infants to a peak of 6-8 mg/dl by 3 days of age and thereafter fall. A rise to 12mg/dl is in the physiological range. In premature infants, peak may be 10-12 mg/dl on the fifth day of life, possibly rising to more than 15mg/dl without any specific abnormality of bilirubin metabolism.

PHYSIOLOGIC MECHANISMS

Distinctive aspects of normal newborn physiology that contribute to neonatal hyperbilirubinemia include:

1. Increased bilirubin synthesis
2. Less effective binding and transportation
3. Less efficient hepatic conjugation and excretion
4. Enhanced absorption of bilirubin via enterohepatic circulation.

INCREASED BILIRUBIN SYNTHESIS

Bilirubin is a breakdown product of hemoglobin. The bilrubin load is greater in neonates because hemoglobin breakdown is two to three times the adult rate and also there is an increase in red blood cells degradation in the marrow even before its release. In addition, bilirubin synthesis in healthy neonates results from greater erythrocyte mass at birth and neonatal red blood cells have a shorter half life compared to adults. The life span of RBCs is less than 70 days for premature infants, 70- 90 days for healthy term infants compared to 120 days in adults.

BINDING AND TRANSPORT

Circulating bilirubin is bound to plasma albumin. It is believed that neuro toxicity associated with hyperbilirubinemia is primarily the result of unbound or “free” bilirubin, so the amount of albumin available for binding is important. A full term infant has lower plasma albumin level than adult and so fewer binding sites for binding the bilirubin.

CONJUGATION AND EXCRETION

The conjugating capacity of normal infants varies greatly, with delayed conjugation and excretion, in some cases, related to the immaturity of the liver cell itself. The activity of uridine diphosphate-glucuronyltransferase (UGT) system in the newborn must be induced. Elevated conjugated bilirubin levels at birth, in cases of severe fetal hemolysis, suggest that STB levels may be necessary to induce the conjugating enzymes.

ENHANCED ENTEROHEPATIC CIRCULATION

Intestinal absorption of bilirubin successfully excreted into the intestine is enhanced by several features of newborn physiology, thereby adding the tendency of newborns to become jaundiced. Conjugated bilirubin as monoglucuronide or diglucuronide is unstable and can be spontaneously or enzymatically hydrolysed to unconjugated bilirubin which can easily be reabsorbed in the intestinal mucosa. In addition absorption is enhanced by the sterility of intestinal contents. Older children and adults have intestinal flora which can metabolize conjugated bilirubin to the readily excretable breakdown products of urobilin and stercobilin. Moreover increased levels of β- glucuronidase can deconjugate bilirubin to form more unconjugated bilirubin which can be absorbed by enterohepatic circulation. Mild alkaline pH and the predominance of monoglucuronides as the main excretion form of bilirubin in the first few days of life of neonate also contributes for increased bilirubin levels.

CLINICAL SIGNIFICANCE

All of the above mentioned factors have a combined effect on potentially increasing serum total bilirubin levels in healthy newborn and a premature baby is even more susceptible. Any pathological process that increases the production or impairs the elimination of bilirubin can exacerbate the normally occurring physiologic jaundice in newborns. In clinical settings such pathologic disorder should be treated appropriately. What remains controversial is the danger posed by increased serum total bilirubin levels encountered in the absence of pathologic disorders[6].

BREAST-MILK JAUNDICE

Breast-milk jaundice is of late onset and has an incidence in term infants of 2%- 4%[5]. Instead of a fall in bilirubin value by day 4, the bilirubin level continues to rise and may reach 20 to 30 mg/dl by 14 days of age. If breast feeding is continued the bilirubin level stay elevated and then falls slowly returning to normal by 4 to 12 weeks. If breast feeding is stopped the bilirubin value will fall rapidly in 48 hours. The mechanism of breast-milk jaundice is unknown but is thought to be due to unidentified factors in breast milk interfering with bilirubin metabolism. Some factors attributed for the cause are pregnane-3α,20β-diol and β-glucuronidase which has not yet been proved.

These infants show good weight gain, have normal liver function test results and show no evidence of hemolysis.

BREAST-FEEDING JAUNDICE

Infants who are breast fed have higher bilirubin levels after day 3 of life compared to formula fed infants. The differences in the levels of bilirubin are usually not clinically significant. The incidence of peak bilirubin levels of more than 12mg/dl in breast fed term infants is 12% to 13%[5]. The main factor thought to be responsible for breast feeding jaundice is a decreased intake of milk that leads to increased enterohepatic circulation.

UNCONJUGATED HYPERBILIRUBINEMIA

Overproduction of bilirubin combined with immature mechanism for conjugation and enhanced intestinal enterohepatic circulation of bilirubin contributes to the development of neonatal jaundice.

CAUSES OF UNCONJUGATED HYPERBILIRUBINEMIA[6]

A. Excessive production of bilirubin (hemolytic disease of newborn)

1. Blood group heterospecificity (incompatibility)
    a. Rh isoimmunization
    b. ABO incompatibility
    c. Minor blood group incompatibility
2. Red blood cell enzyme abnormality
    a. Glucose-6-phosphate dehydrogenase deficiency

b. Pyruvate kinase deficiency

3. Sepsis

4. Red blood cell membrane defects

a. Hereditary spherocytosis

b. Elliptocytosis

c. Poikilocytosis

B. Impaired conjugation or excretion

1. Hormonal deficiency

a. Hypothyroidism

b. Hypopituitarism

2. Disorders of bilirubin metabolism

a. Crigler-Najjar syndrome type I

b. Crigler- Najjar Syndrome type II (Arias syndrome)

c. Gilbert disease

d. Lucey –driscoll syndrome

3. Enhanced enterohepatic circulation

a. Intestinal obstruction, pyloric stenosis

b. Ileus, meconium plug, cystic fibrosis

BILIRUBIN TOXICITY

Excessive bilirubin appears to be a generalized cellular poison[1]. Disruption of membrane function, lowering of action potentials, compromise of energy metabolism, and disturbance of neurotransmitter synthesis and neurotransmission are some of the causes which have been implicated[3].

Neuronal vulnerability to bilirubin would appear to be both gestational and postnatal dependent, possibly reflecting the functional status of the blood brain barrier in the specific area of the brain at the time of the metabolic insult. There is a growing evidence to suggest that the substrate for P-glycoprotein, a plasma membrane efflux pump found on the luminal surface of the brain capillary endothelial cells is considered responsible for limiting entry of certain lipophilic substrates into the CNS[4]. P- Glycoprotein expression has been related to gestational maturity, and may be a factor contributing to the greater vulnerability of the premature brain to bilirubin toxicity.

FACTORS THAT INCREASE SUSCEPTIBILITY TO NEUROTOXICITY ASSOCIATED WITH HYPERBILIRUBINEMIA

1. Asphyxia
2. Hyperthermia
3. Septicemia
4. Hypoalbuminemia

5. Acidosis
6. Caloric deprivation
7. Prolonged hyperbilirubinemia
8. Young gestational age
9. Low birth weight
10. Excessive hemolysis

Attempts to reproduce bilirubin neurotoxicity experimentally in animals point to the importance of coexisting risk factors (such as acidosis, hypoxia, hypercarbia and blood-brain barrier disruption) as being prerequisites for bilirubin toxicity. Agents that interfere with the binding of bilirubin to serum albumin also promote neurotoxicity[1].

THEORIES FOR MECHANISMS OF BILIRUBIN TOXICITY

1. One hypothesis is that lipophilic nature of free bilirubin, on equibilirium with bound bilirubin has access to tissues. Thus when free bilirubin level increases, the levels also increase within the brain tissue saturating membranes and causing precipitation of bilirubin within the nerve cell membrane[6].

   This hypothesis arose to explain the outbreak of kernicterus in premature infants given sulfisoxazole[8].

2. Second hypothesis involves the binding of bilirubin to albumin but also focuses the state of bilirubin available to cross cell membranes. At alkaline pH bilirubin forms a

water-soluble sodium salt, but the solubility of this substance at neutral or low pH is extremely low. Bilirubin is therefore found in plasma as a dianion bound to albumin after dissociation of two hydrogen ions. Bilirubin acid tends to precipitate readily from serum only when the lipid membrane is present suggesting that a supersaturation level of bilirubin acid precipitates in the tissues of icteric infants. This theory provides an explanation for the role that acidosis may play in the development of kernicterus[6].

3. Third theory suggests that bound bilirubin enters brain mainly through damaged blood brain barrier. The importance of a mature blood brain barrier stems from demonstration that the barrier to albumin and bilirubin can be reversibly opened under conditions of vascular injury, abnormal circulation, abnormal osmolarity, hyperthermia and septicemia[6].

4. Recent studies suggest unconjugated bilirubin is a substrate for P- glycoprotein and that the Blood-Brain barrier P-glycoprotein may play a role in limiting the passage of bilirubin into the CNS[9, 10].

CLINICAL BILIRUBIN ENCEPHALOPATHY

The word ‘Kernicterus’ originated as a description of yellow nuclear staining of the brain but has become synonymous with acute and chronic interference with membrane activity and neurological features of what are more correctly termed bilirubin encephalopathy and its sequelae. Three stages have been identified[5];

1. **Stage 1(Early phase) –** characterized by hypotonia, lethargy, high pitched cry, and poor suck.

2. **Stage 2(Intermediate phase)** - Hypertonia of the extensor muscles (with opisthotonus, rigidity, oculogyric crisis, and retrocollis) irritability, fever and may have seizures. Many infants die in this phase. All infants who survive this phase develop chronic bilirubin encephalopathy (clinical diagnosis of Kernicterus)

3. **Stage 3 (Advanced phase)**-Pronounced opisthotonus (hypotonia replaces hypertonia approximately after one week of age) shrill cry, apnea, seizures, coma and death.

CHRONIC BILIRUBIN ENCEPHALOPATHY

The long term features of bilirubin encephalopathy include extrapyramidal disturbances, auditory impairment, upward gaze palsies, dental and enamel dysplasia. The resulting cerebral palsy typically has an element of athetosis which can develop as early as 18 months or may be delayed for several years. High- frequency sensorineural deafness frequently accompanies the cerebral palsy, but may evolve in isolation. Cognitive impairment may occur in bilirubin encephalopathy.

PREDICTING ENCEPHALOPATHY AND REVERSIBILITY OF DAMAGE:

Despite progress made in the clinical management, there is no agreement on what constitutes the “safe” level of bilirubin.

BRAINSTEM EVOKED RESPONSE AUDIOMETRY:

Brainstem Evoked Response Audiometry (BERA) is also called as Auditory Brainstem Evoked Response (ABER) or Auditory Brainstem Response (ABR).

Hyperbilirubinemia affects the auditory pathway causing high frequency hearing loss and frequently in accompanied by cerebral palsy. Since hearing loss is the clinical problem there is a need for accurate assessment of auditory function in infants, young children and person with diminished capacity to reveal their hearing loss. The incidence of moderate to profound hearing loss in high risk infants is reported to be 2.5-5% compared to 1%in normal infants [23].

Among the first clinical application of Brainstem Evoked Response (BER) was the prediction of hearing loss (screening) in infants and young children. First reports of systemic recordings in young infant came around mid 1970s. Since then BERA has been suggested as a screening tool that could identify or predict early effects of hyperbilirubinemia on the central nervous system.

BERA is accurate and non invasive with sensitivity of 100% and specificity of 90.8%[29].

BERA consists of series of seven positive to negative going waves, occurring within 10 milliseconds of stimulus onset[31]. Several system of nomenclature has been devised for the naming of waves but the most commonly used is to label the positive waves in roman numerals from I to VII. The full component of seven waves is not always present in BERA testing. A normal variant is absence of wave II, VI and especially VII[31].

BERA is recorded with electrodes attached to various parts of the head. The electrodes are small cups or discs coated with various materials such as silver, silver chloride and tin. The waves are generated due to the electrical difference generated between the two electrodes[31].

PROCEDURE:

The test should be carried out in a sound proof room and the infant should ideally sleep which can usually be attained after a good feed. In rare instances the infant can be sedated with oral Triclofos 50mg/kg 30 minutes before the procedure[23]. To measure the electrical pulses, small monitoring electrodes are placed on the scalp.

Electrodes:

BERA is recorded from various electrodes attached to various positions on the head.

- ***First electrode*** (noninverting electrode) is placed on the vertex (top of the head) or at the middle of the forehead just below the hairline.
- ***Second electrode*** is placed on the earlobe or mastoid of the ipsilateral ear that is receiving the stimulus.
- ***Third electrode*** is typically placed on the contralateral earlobe, contralateral mastoid, forehead or nape of the neck and serves as a ground electrode.

Before attaching the electrodes the skin must be thoroughly cleaned to remove excess oil, dead skin, and dirt to get good control.

STIMULUS TYPE:

CLICK AND BURST[31]:

Two types of stimulus are used to generate waves in BERA.

1. Click
2. Burst

Click was used in this study. In using BERA to assess the integrity of central auditory pathway click stimuli are generally used because they elicit the clearest wave forms. A sound stimulus is introduced to the infant and the wave pattern generated as electrical impulse through the auditory pathway is measured. Recorded parameters include threshold sensitivity, latency, the interpeak latency, amplitude of the waves, slope of the latency changes with time and magnitude of the stimulus**. Interpeak latencies I-III and I-V are useful in assessing damage from bilirubin[6].**

Brief tone bursts are used when assessing hearing sensitivity in different frequency regions.

Table – 1: BERA- Waves and area of generation[31]

Wave forms	generators
I	VIII nerve
II	Cochlear nucleus
III	Superior olivary nucleus
IV	Lateral lemniscus
V	Inferior colliculus

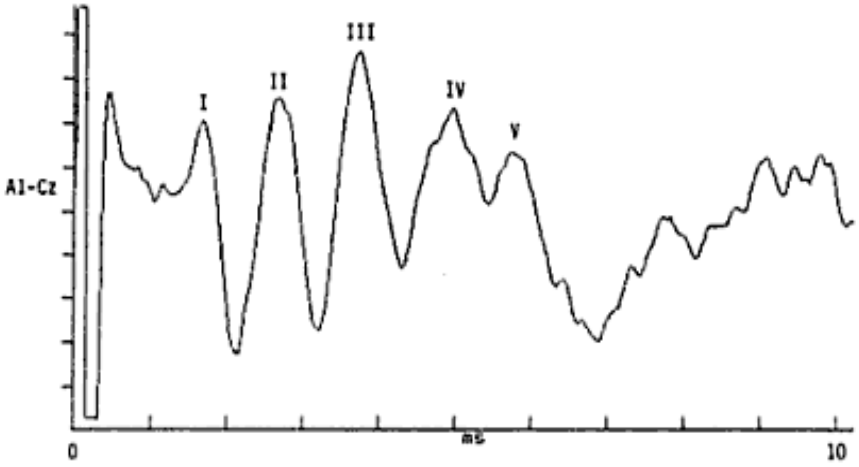

Figure 1: BERA- Waves[31]

Table 2: normal values in BERA[30]

Wave form	Normal value (msec)	Standard deviation
I	1.6	0.2
II	2.8	0.2
III	3.7	0.2
IV	5.1	0.2
V	5.6	0.2
I-III	2.0	0.4
III-V	1.8	0.4
I-V	3.8	0.4

Bilirubin toxicity causes reversible hearing loss, as shown by various studies which show that the BERA abnormality reduces or even normalizes on repeatedly following up the child[27, 14].

TRIVANDRUM DEVELOPMENTAL SCREENING CHART

- Trivandrum developmental screening chart (TDSC) is a screening tool based on 17 selected items from BSID- Baroda Norms (Bailey scale of infant development).

- Each milestone is given a range. The left hand side of the each item represents the age at which 3% of the children would have passed the test and the right end represents 97% passing the test.

- The following milestones are used to identify developmental delay in Triandrum developmental Screening Chart.

    1. Social smile
    2. Eyes follow pen/pencil
    3. Holds head steady
    4. Rolls from back to stomach
    5. Turns head to sound of bell or rattle
    6. Transfers objects hand to hand
    7. Raises itself to sitting position
    8. Standing up by furniture
    9. Fine prehension pellet
    10. Pat a cake
    11. Walks with help
    12. Throws ball
    13. Walks alone
    14. Says two words
    15. Walk backwards
    16. Walk upstairs with help
    17. Points to parts of doll (3 parts)

- The test was designed in Child Developmental Centre, SAT Hospital,Trivandrum.
- It can be used up to 24 months of age.
- Sensitivity of the test is 67% and specificity 79%[22].
- It is widely used as a screening test.
- A vertical line is drawn for the chronological age and if the child fails to attain any of the milestones that falls short on left hand side of the vertical line then it is considered to be a developmental delay.
- Any obvious asymmetry or abnormality is also considered abnormal.

Very few studies have included normal, term newborns with hyperbilirubinemia as the study population even though there are many studies about the auditory evaluation in newborns with hyperbilirubinemia.

A study on Hearing status in neonatal hyperbilirubinemia with Auditory Bainstem Response and Otoacoustic Emission test conducted by Baradaranfar *et al*[11] which included 35 term newborns with hyperbilirubinemia of more than 20 mg/dl found that 26/35 were normal and 9/35 were abnormal (25.7%).

Another study was conducted by Lofti *et al*[12] to know the prevalence of late sensorineural loss in children with history of severe hyperbilirubinemia. It was a cohort study involving 102 children. They found that 6.9% had mild hearing loss and 7.8 % had moderate and 7.8% had severe hearing loss and the BERA abnormality was found to be 22.5%.

A study conducted by N Y Boo *et al*[13]at KualaLumpur showed that the BERA abnormality was 22% in their study population which included 128 newborns who had serum bilirubin of more than 20 mg/dl (>339µmol/l).

In another follow up study, in which follow up was done for 5 years, conducted in China by Chen W X *et al*[14] among new born with jaundice it was found that the BERA abnormality in hemolytic group of jaundice patients was 10% (3/29) at the end of about 3 months (median time interval of the study was 3.2 months) and in non-hemolytic group was 9.1% (9/99). After two years when BERA was repeated in this study population it was found that BERA returned to normal in all except 3 cases. All except 5 among the 128 had a normal neurodevelopmental outcome. They found that the affected cases had only mild motor delay and hypotonia which also returned to normal at 3 years of age. No relation was found between an abnormal initial BERA and the final neurodevelopmental outcome. They concluded that the effect of hyperbilirubinemia is only transient in their population.

In a study conducted in the Department of Pediatrics in PGIMER, Chandigarh[15]in babies who had undergone double exchange transfusion for hyperbilirubinemia it was found that bilirubin abnormality was found in 76% of the cases. Newborns with gestational age more than 35 weeks were involved in the study and the mean serum bilirubin was 37 mg/dl. MRI was abnormal in 61% of the babies. At the end of one year DDST was used for developmental assessment and 60% were found to be affected.

A study done in Lucknow by Agarwal V K *et al*[16]found that among 30 term infants with hyperbilirubinemia BERA abnormality was noted in 56.7% during the initial visit. In 10 cases

the changes reverted on follow up. Three of them were found to have developmental delay when tested by Denver Developmental Screening Test (DDST) at one year of age.

In one another study done in Jaipur[17] in which BERA recording was done in 30 newborns abnormality obtained was 73.3 % and the abnormality persisted in 23.3% of them on follow up.

Various studies have been made to find out whether there is any association with high bilirubin levels and BERA abnormality. Studies by Mukhopadhyay[15] and Agarwal *et al*[16] showed a significant association between high bilirubin values and BERA abnormality. There are also studies conducted by Ziang ZD *et al*[24] which found no association between the two factors.

A study was conducted in England[17] to know the outcomes among newborns who had bilirubin values of more than 25 mg/dl who were treated with phototherapy and exchange transfusion. They were followed up for 2 years and were found to have no adverse neurodevelopmental outcome.

In one of the studies conducted by Psarommatis *et al*[18] to know about the frequency of reversible Auditory Brain Stem Responses in screening failure in high risk newborns 1294 high risk neonatal records were reviewed. It was found that 13.8% have demonstrated abnormal hearing recordings in the initial screening. 64.2% of them had complete recovery and 15% had partial recovery. It concluded that this phenomenon was due to central nervous system maturation and early cochlear implantations should be done only after obtaining reliable behavioral hearing tests.

Hearing assessments in preterm babies with hyperbilirubinemia was also done by various authors. In a study conducted in late preterms with jaundice in Ganga Ram Hospital, Neonatal Division[18], which included a total of 13 neonates it, was found that 6 out of 13 (46%) neonates had audiological abnormalities. It was concluded that auditory neuropathy spectrum is common in preterms with hyperbilirubinemia. Roberts JL *et al*[20] in his study concluded that the abnormal results which were obtained in preterm neonates were due to immaturity of the brain.

In one another prospective study conducted in Dalhousie University, Canada by Jangaard *et al*[19]in newborns having bilirubin equal to or greater than 19 mg/dl, concluded that there was no increase in adverse effects reported previously to be associated with bilirubin toxicity. Associations with developmental delay, attention-deficit disorder, and autism were observed.

Study by Heilmer et al[21] 2010 at Department of Pediatrics, Medical College of Wisconsin, Milwaukee, Wisconsin, USA also concluded that no untoward outcome was found in term healthy infants with moderately severe non-hemolytic hyperbilirubinemia.

STUDY JUSTIFICATION

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The concepts of bilirubin toxicity remain highly controversial. The problem is that bilirubin levels that are toxic to one infant may not be toxic to another, or even to same infant in different clinical circumstances. Currently, major debate surrounds the toxicity of bilirubin in otherwise healthy full term infants and in premature LBW infants[5].

About 3% of the normal term infants have Bilirubin levels of more than 15 mg/dl[5]. No literature is available for the level above which bilirubin toxicity will occur in term neonate.

This study was conducted to know the audiological and developmental outcome of normal term newborn with hyperbilirubinemia of 20 mg/dl or more, who have had intervention for management of hyperbilirubinemia and were not found to have any neurological abnormality by clinical examination during their stay in the hospital.

AIM OF THE STUDY

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MATERIALS AND METHODS

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STUDY PLACE:

1. GOVERNMENT R.S.R.M HOSPITAL, Chennai.

   Government RSRM Maternity hospital, is the maternity hospital of Government Stanley Medical College with an average number of about 11000 deliveries per year. It has a Neonatal Intensive Care unit of level II care. It is an intramural NICU.

2. INSTITUTE OF SOCIAL PEDIATRICS, Stanley medical college, Chennai.

   Institute of Social Pediatrics has a Neonatal Intensive Care Unit of Level II care which is an extramural NICU.

STUDY DESIGN:

Observational Study- longitudinal study

STUDY PERIOD:

January 2010 to August 2011

For the first 7 months, cases were registered.

Follow up of the cases for the next one year.

SAMPLE SIZE AND SAMPLING METHOD:

1. Consecutive sampling method[7] was carried out for this study which is the addition of cases as and when neonates who met the inclusion criteria were admitted.

2. 51 neonates were registered in this study.

A total of 5793 cases were screened during the period of 7 months and 206 cases were found to have yellowish discoloration extending below knee level. Blood investigation for serum bilirubin was done and cases with serum bilirubin of equal to or more than 20 mg/dl were selected. A total of 51 neonates who fit into our inclusion criteria were registered for the study.

The exact percentage of normal term newborns with bilirubin values of 20 mg/dl and above was not available. The only statistics available was that 3% of the normal term infants have bilirubin Levels of more than 15 mg/dl[5]. On using EpiInfo software for calculating sample size assuming that about 1.5% of term newborns may have bilirubin values of 20mg/dl or more it was found that a sample size of 46 cases has a confidence interval of 95%. Adequate sample size was obtained for this study.

INCLUSION CRITERIA:

- Term newborns with birth weight greater than 2500 grams

- Hyperbilirubinemia equal to or more than 20mg/dl

EXCLUSION CRITERIA:

- Sepsis
- Prematurity
- Term IUGR
- Birth asphyxia- APGAR scores of 0-4 at 1 minute or 0-6 at 5 minutes
- Babies with abnormal neurological examination
- Overt endocrinological/metabolic problem/neurologic causes
- Infants critically ill of any cause
- Direct bilirubin greater than 15% of total serum bilirubin
- History of ototoxic drug intake
- Any congenital malformations
- History suggestive of intrauterine infections
- Family history of deafness.

METHODOLOGY:

- 5793 neonates who were born during the study period were screened. Neonates less than 2.5 kg were excluded. Term babies were screened for jaundice and cases with yellowish discoloration extending below knee were subjected to serum bilirubin levels. Babies with serum bilirubin of equal to or more than 20 mg/dl were further selected after applying the exclusion criteria. Babies fulfilling all the inclusion criteria were involved in the study.

- Informed consent was obtained from parents.

- Demographic data, antenatal history comprising of past history, family history of any hearing abnormality, history of any fever with rashes and lymphadenopathy, ototoxic drug exposure were recorded.

- In natal history, history for term/preterm, birth weight, mode of delivery, and APGAR score were recorded.

- Postnatal history of any NICU admission was noted.

- Clinical examination was carried out for the babies. Babies with congenital malformations of the external ear, any abnormal facies and abnormal neurological examination were ruled out.

- Bilirubin values were estimated and babies with total serum bilirubin levels of equal to or more than 20 mg/dl were included in the study.

- Mode of treatment was whether phototherapy or exchange transfusion was given was noted.

- Cause for jaundice was noted. It was grouped into Rh incompatibility, ABO incompatibility and other causes.

- Thyroid profile to rule out hypothyroidism was done.

- Babies were planned for BERA (Brainstem Evoked Response Audiometry) after discharge and abnormality in BERA if present was noted. If abnormality was detected babies were referred to an audiologist.

- BERA was repeated in the above population before 3 months to see if the changes persisted or had resolved.

- Babies were also followed up using Trivandrum developmental screening chart (TDSC) at 3, 6, 9, 12 months of age and abnormalities, if any were noted.

- All details were analyzed using appropriate statistical methods.

STATISTICAL ANALYSIS:

- Demographic variables like parity, sex of the baby, weight of the baby, mode of delivery, type of treatment and abnormal values in BERA were analyzed using SPSS 16 for windows and is given in percentage.

- Association between bilirubin values with parity, sex of the baby, weight, mode of delivery and type of treatment was analyzed and given in percentage.

- For finding the association between bilirubin value and other parameters chi-square test was used.

- Values of chi-square more than 3.84 and p value of less than 0.05 were taken as statistically significant.

- Logistic regression was done whenever necessary.

OBSERVATION AND RESULTS

OBSERVATION AND RESULTS

- Among the 51 babies who were included in the study after screening 5793 babies during the 7 months period 26 babies were born to primigravida (51%) and 25 were born to multigravid mothers (49%) (figure 2)

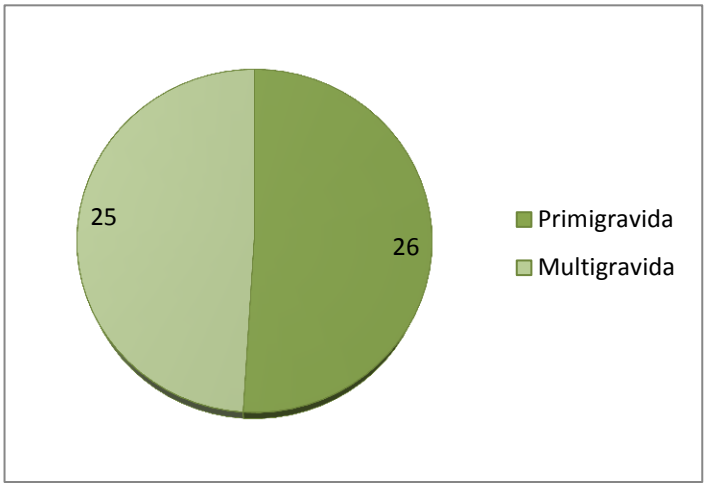

Figure 2: Parity of the mothers of study population

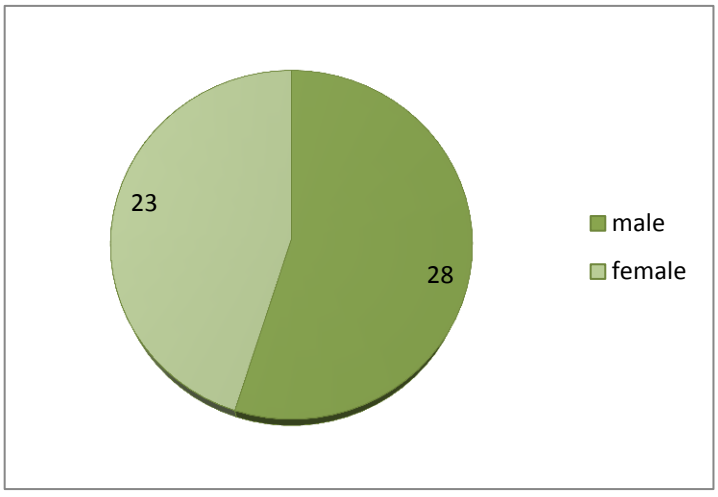

Figure 3: sex distribution in the study population

- From figure 3 which shows the sex distribution in the study population, male babies constituted 28/51 (54.9%) and female babies 23/51 (45.1%).
- From figure 4 showing weight distribution, 25/51 babies (49%) were between 2500-2999 grams, 21/51 (41.2%) were between 3000-3499 grams and 5/51 (9.8%) were of weight more than 3500 grams.

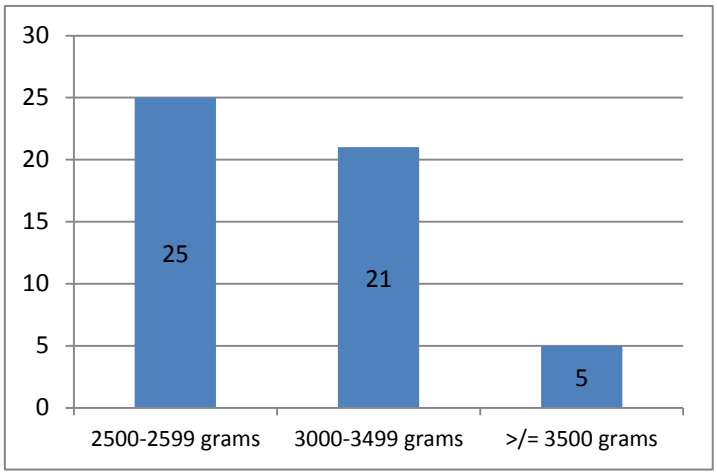

Figure 4: distribution of weight in the study population

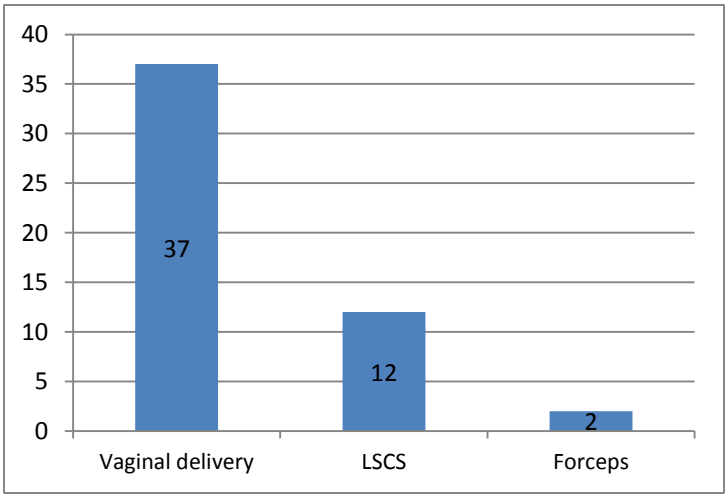

Figure 5: Mode of delivery of the babies

- Analyzing the Mode of delivery (figure 5), 37/51 (72.5%) were born of normal vaginal delivery, 12/51 (23.5%) were born of LSCS and 2/51 (3.9%) were born of forceps delivery.
- 40/51(78.4%) had total serum bilirubin value between 20-24.9 mg/dl whereas 11/51 cases had bilirubin value of more than 25 mg/dl (21.6%) (Figure 6).

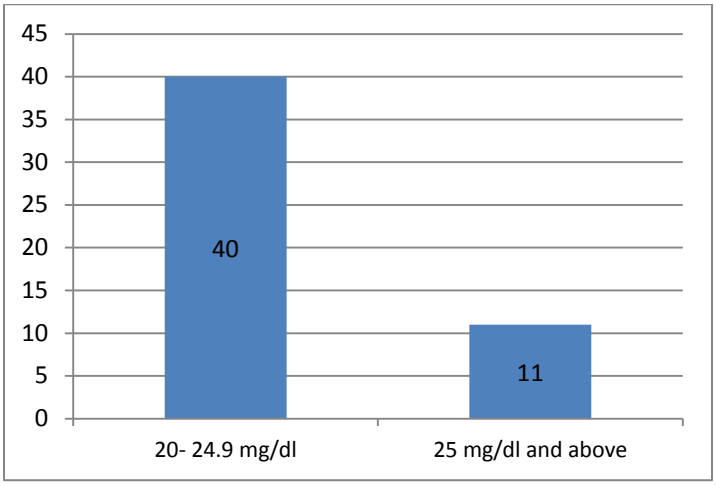

Figure 6: Serum Bilirubin values in study population

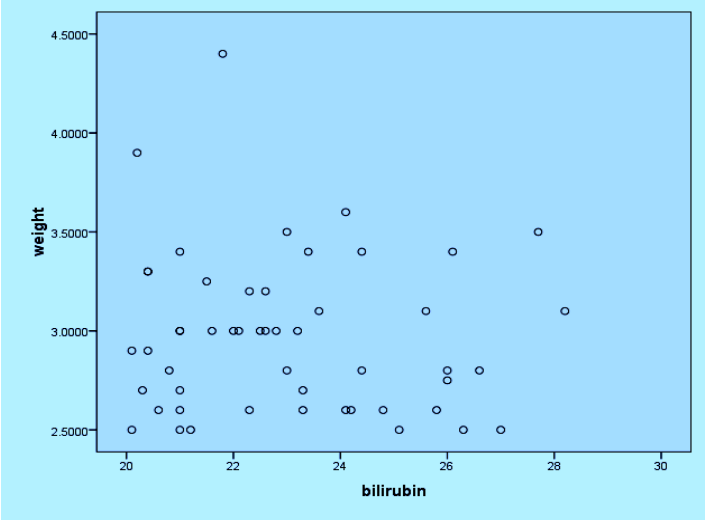

Figure 7: Total serum bilirubin distribution against weight of the babies

- The mean total serum bilirubin value was 23.02 mg/dl, median 22.60 mg/dl, mode was 21 mg/dl, with a standard deviation of 2.22 mg/dl, maximum value was 28 mg/dl and minimum value was 20 mg/dl.
- 12/51(23.5%) cases were due to Rh incompatibility, 17/51 cases (33.3%) due to ABO incompatibility and 22/51 (43.1%) due to other causes (Figure 8).

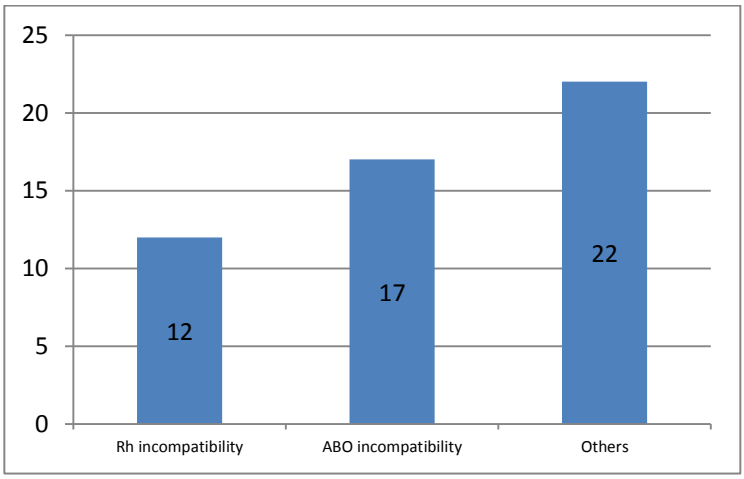

Figure 8: cause of hyperbilirubinemia

- From figure 9 showing treatment of the study population, 16/51 (31.3%) underwent exchange transfusion, whereas 35/51 (68.6%) had phototherapy.

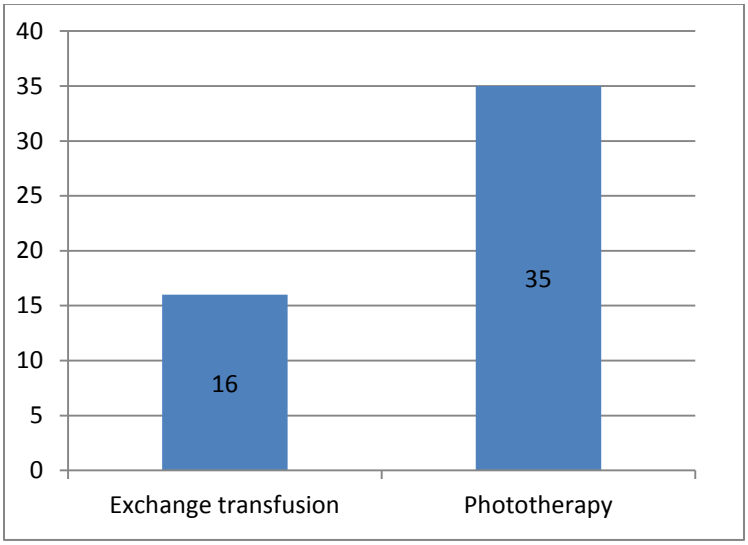

Figure 9: treatment underwent by the study population

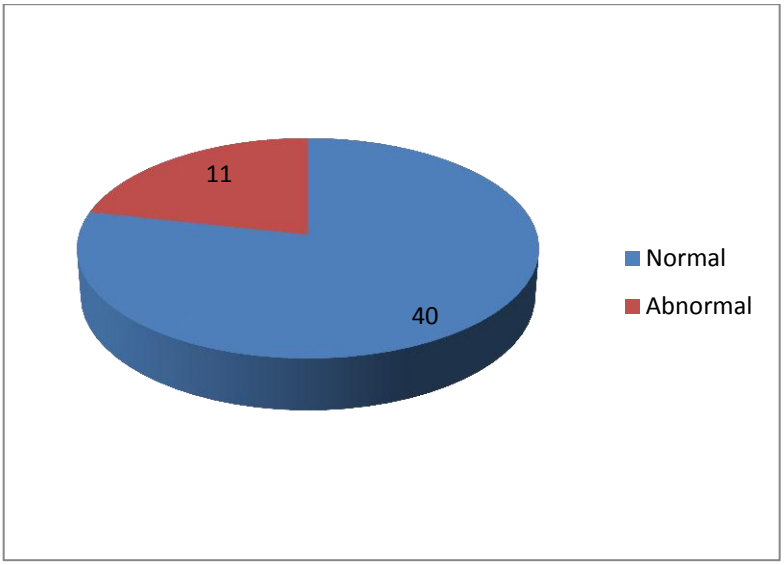

Figure 10: BERA abnormalities at the time of discharge

- BERA abnormalities were noted in 11/51 (21.6%) (Table 3) of the babies of which 4/11 had unilateral and 7/11 had bilateral abnormalities.

Table 3: BERA abnormality at the time of discharge

BERA	frequency	percent
Normal	40	78.4
Abnormal	11	21.6
total	51	100

- In BERA done at the time of discharge, I-III interval was prolonged in 9/51 cases (17.6%) and was normal in 42/51 (82.4%) of the cases.(Table 4)

Table 4: I-III interval prolongation at discharge BERA

BERA-I-III interval	frequency	percent
Normal	42	82.4
Abnormal	9	17.6
	51	100

- From Table 5, In BERA done at the time of discharge, I-V interval was prolonged in 11/51 (21.6%) of the cases (both unilateral and bilateral) and 7/11 had bilateral abnormalities.

Table 5: I-V interval prolongation in BERA at discharge

BERA–I-V interval	frequency	percent
Normal	40	78.4
Abnormal	11	21.6
total	51	100

- The mean age of BERA examination after discharging the babies was 10.18 days and median age was 10 days. Earliest age was 6 days and the maximum age of testing for the first time was 18 days.
- On follow up BERA I-III wave abnormality was noted in only in 4/51 (7.8%)of the cases and 47/51 (92.1%) had normal waves(Table 6)

Table 6: BERA I-III interval prolongation on follow up

BERA I-III interval	frequency	percent
Normal	47	92.1
Abnormal	4	7.8
total	51	100

- From table 7, on following up with repeat BERA I-V abnormality was persisting only in 5/51 (9.8%) and 46/51(90.2%) were normal.

Table 7: BERA I-V interval prolongation on follow up

BERA I-V interval	frequency	percent
Normal	46	90.2
Abnormal	5	9.8
total	51	100

- The mean age of repeat BERA was 77.55 days with a minimum age of 68 days and maximum age of 93 days.

- On comparing total serum bilirubin values with both Unilateral/bilateral BERA abnormalities ‘p’ value was found to be statistically significant (‘p’ value-0.001) indicating higher the bilirubin value more chances of having BERA abnormality.(Table 8)

Table 8: Effect of value of bilirubin on BERA abnormality at the time of discharge

Bilirubin	BERA		Total
	normal	abnormal	
20-24.9 mg/dl	36	4	40
>/= 25 mg/dl	4	7	11
total	40	11	51

'p' value- 0.001- highly significant
Chi-square value-14.672- significant.

- On comparing total serum bilirubin with final BERA abnormality (Table 9), 'p' value was statistically significant ('p' value- 0.008), even after reversal of abnormalities in some cases.

Table 9: Effect of value of bilirubin on BERA abnormality at the time of follow up

Bilirubin	BERA		Total
	Normal	abnormal	
20-24.9 mg/dl	39	1	40
>/= 25 mg/dl	7	4	11
total	46	5	51

'p' value- 0.008- significant
Chi-square test- 11.591 significant.

- On comparing BERA abnormalities with the cause of jaundice,

(Table 10) chi-square value was not statistically significant

(Chi- square value- 1.520), meaning the cause of jaundice doesn't relate to BERA abnormality.

Table 10: Effect of cause of jaundice on BERA abnormality

cause	BERA		Total
	Normal	abnormal	
Rh incompatibility	9	3	12
ABO incompatibility	12	5	17
Others	19	3	22
total	40	11	51

Chi-square value- 1.520- not significant.

- On comparing treatment with BERA abnormality, p value was found to be statistically significant ('p' value- 0.002) (Table 11).

Table 11: Effect of treatment on BERA abnormality

Treatment	BERA		Total
	Normal	abnormal	
Exchange transfusion	8	8	16
Phototherapy	32	3	35
total	40	11	51

'p' value- 0.002- Statistically significant.

Chi-square value- 11.141- significant.

- It was found in the study that there was reversibility in BERA abnormalities in 54.54% of the cases. Out of the 11 neonates who had BERA abnormality detected at the time of discharge only 5 had persisting BERA changes on follow up by third month.

- On comparing BERA abnormality with weight of the baby(table 12)., Chi-square test did not give significant values (chi-square value- 0.174)

Table 12: relation between weight of the infant and BERA abnormality

Weight	BERA		Total
	Normal	abnormal	
2500-2999 grams	19	6	25
3000- 3499 grams	17	4	21
>/= 3500 grams	4	1	5
total	40	11	51

Chi- square value- 0.174 – not significant

- On comparing mode of delivery with BERA abnormalities, chi- square value was 0.887 which is not significant (Table 13). Similarly on comparing BERA abnormalities with the sex of the baby, 'p' value was 1.000 and is not significant (Table 14).

Table 13: Effect of mode of delivery on BERA abnormality:

Mode of delivery	BERA		Total
	Normal	abnormal	
Vaginal	28	9	37
LSCS	10	2	12
forceps delivery	2	0	2
total	40	11	51

Chi-square value- 0.887- not significant

Table 14: Effect of sex of the baby on bilirubin abnormality

Sex of the baby	BERA		Total
	Normal	abnormal	
Male	22	6	28
Female	18	5	23
total	40	11	51

'p' value- 1.000 not significant

- On comparing parity with BERA abnormality 'p' value was not significant ('p' value- 0.499).

- In conclusion significant p value was obtained between total serum bilirubin, mode of treatment and BERA abnormalities.

- No significance was found in our study between BERA abnormalities and parity, sex, weight and mode of delivery.

- Only two factors had significance with BERA abnormalities namely level of bilirubin and type of treatment. On computing logistic regression for these two factors following the result was obtained.

- On performing a binary logistic regression in SPSS software, only bilirubin value [Exp(B) 7.000] was found to be significant compared to treatment which had a Exp(B) value of 0.375 and thus lost its significance.

- This significance may be related to the fact that exchange transfusion is being done for higher bilirubin values and there has been a statistical significance between bilirubin value and BERA abnormality.

FOLLOW UP OF INFANTS FOR DEVELOPMENTAL MILESTONES BY TRIVANDRUM DEVELOPMENTAL SCREENING CHART (TDSC):

- On following up the babies with Trivandrum Developmental Screening Chart, at the third month for the attainment of various milestones, head control was achieved by all the neonates. (Table 15)

Table 15: TDSC abnormality on follow-up at third month

TDSC	frequency	percent
Normal	51	100
Abnormal	0	0
Missed cases	0	0

- By the 6th month all infants who came for follow up achieved the required milestones and there was no developmental delay noted. Two cases were lost during the follow-up (table 16).

Table 16: TDSC abnormality on follow-up at sixth month

TDSC	**frequency**	**percent**
Normal	49	96.1
Abnormal	0	0
Missed cases	2	3.9

- No developmental delay was found in infants by Trivandrum developmental screening chart during their ninth month visit. Five cases were lost during the follow-up during this period of study (Table 17).

Table 17: TDSC abnormality on follow-up at ninth month

TDSC	frequency	percent
Normal	46	90.2
Abnormal	0	0
Missed cases	5	9.8

- At the end of one year, no developmental abnormality was found in the infants using Trivandrum developmental screening chart. Five cases were lost to follow-up at the end of the study (Table 18).

Table 18: TDSC abnormality on follow-up at one year

TDSC	frequency	percent
Normal	46	90.2
Abnormal	0	0
Missed cases	5	9.8

- On analyzing total serum bilirubin value with any delay in attaining milestones, ‘p’ value was not significant ('p'=1.000), even on assuming that all missing cases could have had developmental delay. Thus no significance was obtained between total serum bilirubin levels and the attainment of various milestones by using Trivandrum developmental screening chart for these infants.

DISCUSSION

DISCUSSION

Total number of newborns studied in our study was 51. In our study the BERA abnormality in normal risk term newborn with hyperbilirubinemia of 20 mg/dl or more was found to be 21.6%. 'p' value was significant on comparing bilirubin levels and BERA abnormalities. On following the developmental milestones of these newborn for one year using Trivandrum developmental screening chart no delay in milestones was noted. There was a reversibility of BERA abnormalities in our study by 54.54%.

NEONATAL HYPERBILIRUBINEMIA AND BRAINSTEM EVOKED RESPONSE AUDIOMETRY ABNORMALITY:

BERA abnormalities noted for the cases of hyperbilirubinemia were 21.6% at the time of discharge. Table 19 shows the comparison of our study with other studies done between the neonatal hyperbilirubinemia and BERA abnormality.

On comparing our study with studies made at various countries, Baradaranfar *et al*[11], 2011 found a BERA abnormality of 25.7%, Lotfi *et al* [12], 2010 had BERA abnormality of 22.5%. Results of M.Oake, N Y Boo *et al*[13] was 22% and Ziang Z D *et al*[24]2009 found BERA abnormality in 28% of their study population.

All these studies are comparable to our study and the results are also comparable.

Table 19: Comparison of various studies of neonatal hyperbilirubinemia and BERA abnormality with our study

Study	Percentage of BERA abnormality
Present study	**21.6**
INTERNATIONAL STUDIES	
Baradaranfar *et al*[11], 2011	25.7
Lotfi *et al*[12], 2010	22.5
M.oake, N Y Boo *et al* [13]1994	22
Ziang Z D *et al*[24], 2009	28
Chen W X *et al*[14], 2006	9.37
NATIONAL STUDIES	
Mukhopadhyay *et al*[15], 2011	76
Sharma *et al*[25], 2006	73.3
Agwarwal V K *et al*[16], 1998	56.7

On comparing with Chen W X *et al*[14] 2006, the BERA abnormality found on the study was 9.37% which is lower than our study.

Regarding studies done in India, no studies were available from South India. Studies have been done only in Northern India till now. On comparing the study done by Mukhopadhyay *et al*[15] 2011, the BERA abnormality found by that study was 76%. The possible explanation for the disparity could be because of the fact that the study population included in the study were babies of more than 35 weeks of gestation (preterm also) and the mean serum bilirubin value of the study was 37mg/dl which is far higher than our study which had a mean serum bilirubin of 23.02 mg/dl.

On comparing with another Indian study, Sharma *et al*[25], 2006, the BERA abnormality was 73.3%. A possible explanation for this disparity may be because in this study the BERA was conducted at the time of peak bilirubin levels and in our study it was done only at discharge.

CORRELATION BETWEEN BERA ABNORMALITIES AND SERUM BILIRUBIN LEVELS:

In our study there was a significant 'p' value for the association between serum total bilirubin levels and BERA abnormalities. Our study comparison with other studies is shown in Table 20.

Table 20: Comparison with other studies of correlation between BERA abnormalities and serum bilirubin levels

Study	Result
Mukhopadhyay *et al*[15], 2011	Significant association
Agarwal *et al*[16], 1998	Significant association
Silva *et al*[26], 2009	No correlation
Ziang ZD *et al*[24], 2009	No correlation
Present study	**Significant p value**

Mukhopadhyay *et al*[15], 2011 and Agarwal *et al*[16]1998 also had similar results suggesting association between serum bilirubin levels and BERA abnormalities.

Ziang Z D *et al*[24], 2007, on his study on term infants with hyperbilirubinemia found that although acute ototoxic effect of hyperbilirubinemia tends to be more significant at higher rates than lower rates, auditory impairment do not closely increase with increase in serum bilirubin values.

Studies by Silva *et al*[26] and Ziang Zd *et al*[24], 2009 did not find any association between serum bilirubin and BERA abnormalities.

REVERSIBILITY OF BERA ABNORMALITIES:

Table 21: Comparison between our study and others about reversibility of BERA abnormalities.

Study	Result
Present study	**54.54% recovery**
Psarommatis *et al*[27], 2011	64.2% recovery
Sharma *et al*[25], 2006	68.18% recovery
Chen W X *et al*[14], 2006	72.72% recovery

In our study BERA abnormality was reversed in 54.54% of the babies. Comparing this with other studies(Table 21) , Psarommatis *et al*[27], 2011 in his study found that 64.2% of the babies with hyperbilirubinemia with BERA abnormalities reverted on further follow up.

On comparing with the study by Chen W X *et al*[14] study, 2006, BERA abnormality returned to normal in about 72.72% of the babies. These babies were followed up to 2 years of age and at the end of 2 years 72.72% babies with initial abnormal BERA had normal BERA.

On comparing with the study done by Sharma *et al*[25], 2006, BERA abnormality reversed in 68.18 % of babies.

FOLLOW-UP OF DEVELOPMENTAL MILESTONES:

Table 22: Comparison of developmental outcome of our study and others

Study	Result
Thomas B Newmann *et al*[17], 2006	Not associated with any abnormal neurodevelopmental outcome
Heilmer *et al*[21], 2010	No abnormality was noted
Chen W X *et al*[14], 2006	3.9% had abnormal neurodevelopmental outcome
Agarwal *et al*[16], 1998	10% had abnormal DDST
Present study	**NO delayed milestones were noted in any cases.**

In our study developmental screening was done with Trivandrum Developmental Screening Chart (TDSC) and all babies passed the test successfully.

Comparing our study with study done by Thomas B Newmann *et al*[17], 2006, who also found that there was no abnormal Neurodevelopmental outcome for babies with bilirubin value of more than 25 mg/dl who were treated with exchange transfusion. In this study neurodevelopmental outcome was assessed by child psychologists by Wechsler Preschool and

Primary Scale of Intelligence–Revised (WPPSI-R) and the Beery–Buktenica Developmental Test of Visual-Motor Integration and no abnormality were detected in the children.

Study by Heilmer *et al*[21] 2010 at Department of Pediatrics, Medical College of Wisconsin, Milwaukee, Wisconsin, USA also concluded that there was no untoward outcome found in term healthy infants with moderately severe non-hemolytic hyperbilirubinemia. Assessment was done by Bailey Scales of Infant development II test, speech evaluation, behavioral hearing test and a neurological examination.

On comparing our study with that done by Chen W X *et al*[14] it was found that 3.6% of the babies on follow-up were found to have neurodevelopmental abnormality.

In this study all had regular physical, neurologic, visual, and auditory evaluation until 3 years of age.

Study by Agarwal *et al*[16] 1998 found that the abnormality was 10%. But in this study Denver Developmental Screening Test was used and not Trivandrum developmental screening chart.

CONCLUSION

CONCLUSION

Analysis was done for auditory abnormalities for term newborn with bilirubin values of 20mg/dl or more, who have had interventions for the management of hyperbilirubinemia and had no abnormal neurological examination during their stay in the hospital. Analysis of the study results show that BERA abnormalities were present in 21.6% of term newborns with hyperbilirubinemia as the only risk factor at the time of discharge.

Though there is a reversibility of BERA abnormality in 54.54% of these neonates with hyperbilirubinemia, abnormality still persists in 9.8% of these neonates by 3 months of age.

No obvious developmental delay was found out by using Trivandrum developmental screening chart in these infants on one year followup.

It is therefore necessary that all term newborns with bilirubin values of 20mg/dl or more, even if not associated with any other risk factor, be screened with BERA and these babies be followed up regularly to find if they have persistent abnormalities so that they can be effectively managed..

No significant association was found between BERA abnormalities and sex, weight and the cause of hyperbilirubinemia.

LIMITATIONS AND SUGGESTIONS

LIMITATIONS AND SUGGESTIONS

- BERA was done after discharge and not at peak of hyperbilirubinemia due to operational difficulties.

- Follow up was done for one year only. Further follow-up would be helpful for determining long term effects of hyperbilirubinemia in normal risk term newborns.

- Suggestions :

    - The study can be performed with lower bilirubin value to know whether further lower levels may have BERA abnormalities.

    - Period of follow up could be longer.

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APPENDIX

APPENDIX – 1

PROFORMA

FOLLOW UP OF TERM NEWBORN WITH HYPERBILIRUBINEMIA FOR ONE YEAR - FOR DEVELOPMENTAL AND AUDITORY ABNORMALITY

Baby of: name:

Sex:

Address:

Phone number:

Antenatal history:

Score: G P L A: 1. Primigravida 2. Multigravida

Past history: 1. Significant 2. Not significant

Family history of any hearing impairment at childhood period:

1. Significant 2. Not significant

Present pregnancy:

H/o fever 1st trimester:

2nd trimester:

3rd trimester: 1. Significant 2. Not significant

H/o any radiation exposure: 1. Significant 2. Not significant

H/o any systemic diseases: 1. Significant 2. Not significant

H/o any ototoxic drug ingestion: 1. Significant 2. Not significant

Natal history:

Term : yes/no

Birth wt: <2500gms/ >2500 gms ; gms

1. 2500- 2499 grams
2. 3000-3499 grams
3. 3500 grams and above

Mode of delivery :

1. vaginal
2. LSCS
3. forceps
4. vacuum

Whether cried immediately after birth : yes /no

APGAR : 1”

5”

Postnatal history

H/o not crying immediately after birth: yes/no

H/o NICU admission : yes/no

If yes duration :

Clinical examination:

Jaundice level by clinical examination: Below Knee 1. Yes 2. No

Any congenital abnormality : 1. Yes 2. No

Abnormal Clinical Examination: 1 Yes 2. No

Bilirubin Level:

Date			
Bilirubin level			

:

Whether exchange transfusion done : 1.Yes 2. No

Whether bilirubin level >20mg% : 1. Yes 2. No

Thyroid profile : 1. Normal 2. abnormal

Cause of hyperbilirubinemia

1. Rh incompatibility
2. ABO incompatibility
3. Others

BERA:

Done on day :

Result : 1. Normal 2. Abnormal

I-III wave abnormality 1. Normal 2.Abnormal

I-V wave abnormality 1. Normal 2.Abnormal

Other comments:

If abnormal repeat BERA: 1. Normal 2. Abnormal

Date:

I-III wave abnormality 1.Normal 2. Abnormal

I-V wvae abnormality 1.Normal 2.Abnormal

Other comments:

Trivandrum Developmental Screening Test:

1st follow-up

Date :

Attained milestones: 1) yes 2) no

2nd follow-up

Date

Attained milestones: 1) yes 2) no

3rd follow-up

Date

Attained milestones: 1) yes 2) no

4th follow-up

Date

Attained milestones: 1) yes 2) no

Inference

BERA : 1. Normal

1. Abnormal

TDST : 1. Normal

2. Abnormal

APPENDIX- 2

MASTER CHART

	parity	sex	wt	MOD	bilirubin	treatment	cause	A	B	C	D	E	F	G	tdst	threemonths	sixmonths	ninemonths	twelvemonths
b/o nazeema	2	1	1	3	1	2	3	1	1	1	1	1	1	1	1	1	1	1	1
b/omuniamma	1	2	2	1	2	1	2	2	2	2	2	2	2	2	1	1	1	1	1
b/o kowsalya	2	1	1	2	2	1	1	1	2	2	2	1	1	1	1	1	1	1	1
b/o kumari	1	1	1	1	2	1	2	1	1	1	1	1	1	1	0	1	0	0	0
b/o parveen	2	1	1	1	2	1	3	2	2	2	2	1	2	2	1	1	1	1	1
b/o bhuvaneshwari	2	2	2	1	1	2	2	1	1	1	1	1	1	1	1	1	1	1	1
b/o tharif	2	1	2	1	1	2	3	1	1	1	1	1	1	1	1	1	1	1	1
b/o lalitha	1	1	3	2	1	2	3	1	1	1	1	1	1	1	1	1	1	1	1
b/o meena nandakumar	1	1	1	1	1	2	2	1	1	1	1	1	1	1	1	1	1	1	1
b/o vijaya	2	2	2	1	1	1	2	2	2	1	2	1	2	2	1	1	1	1	1
bv/o selvi	1	2	1	1	1	2	3	1	1	1	1	1	1	1	1	1	1	1	1
b/o shobana	1	1	1	1	1	2	3	1	1	1	1	1	1	1	1	1	1	1	1
b/o satya	1	1	2	2	1	2	3	1	1	1	1	1	1	1	1	1	1	1	1
b/o parimala	1	2	1	2	1	2	3	1	1	1	1	1	1	1	1	1	1	1	1
b/o najma	1	2	1	1	1	2	3	1	1	1	1	1	1	1	1	1	1	1	1
b/o kalaiarasan	2	2	3	1	2	1	2	2	2	2	2	1	1	1	1	1	1	1	1
b/o kalpana	1	1	2	2	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
b/o rekha	2	2	1	1	1	2	3	1	1	1	1	1	1	1	1	1	1	1	1
b/o loga	1	2	1	1	1	2	3	1	2	2	2	2	1	1	1	1	1	1	1
b/o murugadha	1	1	1	1	1	2	2	2	2	2	2	1	1	1	0	1	1	0	0
b/o rekha	2	2	1	1	2	1	3	1	1	1	1	1	1	1	1	1	1	1	1
b/o ammamulu	2	2	1	1	1	2	2	1	1	1	1	1	1	1	1	1	1	1	1
b/o anushya	1	2	2	1	1	2	3	1	1	1	1	1	1	1	1	1	1	1	1
b/o sabiyamani	1	2	1	1	2	1	1	1	2	2	2	1	1	1	1	1	1	1	1
b/o nasrin	1	2	2	1	1	2	3	1	1	1	1	1	1	1	1	1	1	1	1
b/o sangeetha	2	1	1	1	1	2	1	1	1	1	1	1	1	1	1	1	1	1	1

	parity	sex	wt	MOD	bilirubin	treatme	caus	A	B	C	D	E	F	G	tdst	threemonths	sixmonths	ninemonths	twelvemonths
b/o nargese	1	1	1	1	1	2	3	1	1	1	1	1	1	1	1	1	1	1	1
b/o mohana	2	2	2	1	1	2	2	1	1	1	1	1	1	1	1	1	1	1	1
b/o anitha	2	2	2	1	1	2	1	1	1	1	1	1	1	1	0	1	0	0	0
b/o kalaiselvi	2	2	2	1	1	2	3	1	1	1	1	1	1	1	1	1	1	1	1
b/o rita	1	1	2	2	2	1	1	2	2	2	2	2	2	2	1	1	1	1	1
b/o padma	2	1	1	1	1	1	2	1	1	1	1	1	1	1	1	1	1	1	1
b/o karpagam	2	1	1	2	2	1	1	1	1	1	1	1	1	1	1	1	1	1	1
b/o roja	1	2	1	1	1	2	1	1	1	1	1	1	1	1	1	1	1	1	1
b/o nathiya	1	1	2	1	1	2	3	1	1	1	1	1	1	1	1	1	1	1	1
b/oshobana	1	1	2	1	1	2	3	1	2	1	2	1	1	1	1	1	1	1	1
b/o sangeetha	1	1	1	1	1	2	2	1	1	1	1	1	1	1	1	1	1	1	1
b/o gunaselvi	2	1	1	1	1	1	2	1	1	1	1	1	1	1	0	1	1	0	0
b/o latha	2	2	1	1	1	2	3	1	1	1	1	1	1	1	1	1	1	1	1
b/o amutha	2	1	1	1	1	2	1	1	1	1	1	1	1	1	1	1	1	1	1
b/o pavithra	2	2	2	2	1	2	1	1	1	1	1	1	1	1	1	1	1	1	1
b/o bindhu	1	2	3	2	1	2	3	1	1	1	1	1	1	1	1	1	1	1	1
b/o devagi	2	2	3	2	1	2	3	1	1	1	1	1	1	1	1	1	1	1	1
b/o bhuvanesh	1	1	3	1	1	2	2	1	1	1	1	1	1	1	0	1	1	0	0
b/o vighneshw	2	1	2	3	1	2	3	1	1	1	1	1	1	1	1	1	1	1	1
b/o maheshwa	2	1	2	2	1	2	2	1	1	1	1	1	1	1	1	1	1	1	1
b/o jeeva	2	1	2	1	1	2	2	1	1	1	1	1	1	1	1	1	1	1	1
b/o syed farid	1	1	2	1	2	1	1	1	1	1	1	1	1	1	1	1	1	1	1
b/o dhanalaksh	2	2	2	2	1	2	1	1	1	1	1	1	1	1	1	1	1	1	1
b/o deepa	1	1	1	1	2	1	2	2	2	2	2	2	2	2	1	1	1	1	1
b/o nalini	1	1	2	1	1	1	2	1	1	1	1	1	1	1	1	1	1	1	1

APPENDIX – 3

KEYS TO MASTER CHART

Parity

1- Primigravida
2- Multigravida

Sex of the newborn

1- Male
2- Female

Weight of the baby

1- 2500-2999 grams
2- 3000- 3499 grams
3- 3500 grams and above

MOD- mode of delivery

1- Vaginal delivery
2- LSCS
3- Forceps

Bilirubin – serum total bilirubin

1- 20- 24.9 mg/dl
2- 25 mg/dl and above

Treatment

1- Exchange transfusion
2- Phototherapy

Cause of hyperbilirubinemia

1- Rh incompatibility
2- ABO incompatibility
3- Other causes

A – only bilateral abnormality

1- Normal
2- Abnormal

B – both unilateral and bilateral abnormality included

1- Normal
2- Abnormal

C – I-III wave prolongation- BERA at discharge

1- Normal
2- Abnormal

D – I-V wave prolongation- BERA at discharge

1- Normal
2- Abnormal

E- I-III wave prolongation- BERA at follow- up

1- Normal
2- Abnormal

F – I-V wave prolongation- BERA at follow- up

1- Normal
2- Abnormal

G – BERA result on follow-up

1- Normal
2- Abnormal

TDST- Trivandrum Developmental Screening Test Result

0- Missed cases
1- Normal
2- Abnormal

Threemonth- 3rd month TDST result

0- Missed cases
1- Normal
2- Abnormal

Sixmonth- 6th month TDST result

0- Missed cases
1- Normal
2- Abnormal

Nine month- 9th month TDST result

0- Missed cases
1- Normal
2- Abnormal

Twelvemonth- one year TDST result

0- Missed cases
1- Normal
2- Abnormal

APPENDIX – 4

CERTIFICATE FOR APPROVAL OF ETHICAL COMMITTEE

To
Dr.M. Vinodh, PG in MD(Paed)
Dear **Dr.M. Vinodh, PG in MD(Paed)**
The Institutional Ethics Committee reviewed and discussed your application for approval of the project entitled

"Follow up of New Born with Hyperbilirubinemia for one year "

The following members of the ethics committee were present at the meeting held on 28.01.2010 at the Council Hall, Stanley Medical College, Chennai-1 at 10.00AM

Dr.C.B.Tharani, Director of Pharmacology,
Madras Medical Collge, Chennai-3 - Chairman of the Ethics Committee
Dr.S. Chitra, Vice-Principal,
Stanley Medical College, Chennai – 1- Member Secretary of the Ethics Committee

MEMBERS

Dr.Jayanthi
Prof.of Medical Gastroenterology
Dr.Madhavan
Prof.of Pharmacology
Dr.E.Dhandapani
Prof.of Medicine
Dr.Sujatha Sridharan
Prof.of Paediatrics
Thiru.Pachaiappan,
Junior Administrative Officer,
Thiru.A. Senthil Manoharan,
Advocate

We approve the project to be conducted in its presented form.

The Institutional Ethics Committee/Independent Ethics Committee expects to be informed about the progress of the study, any SAE occurring in the course of the study, any changes in the protocol and patient information/informed consent and asks to be provided a copy of the final report.

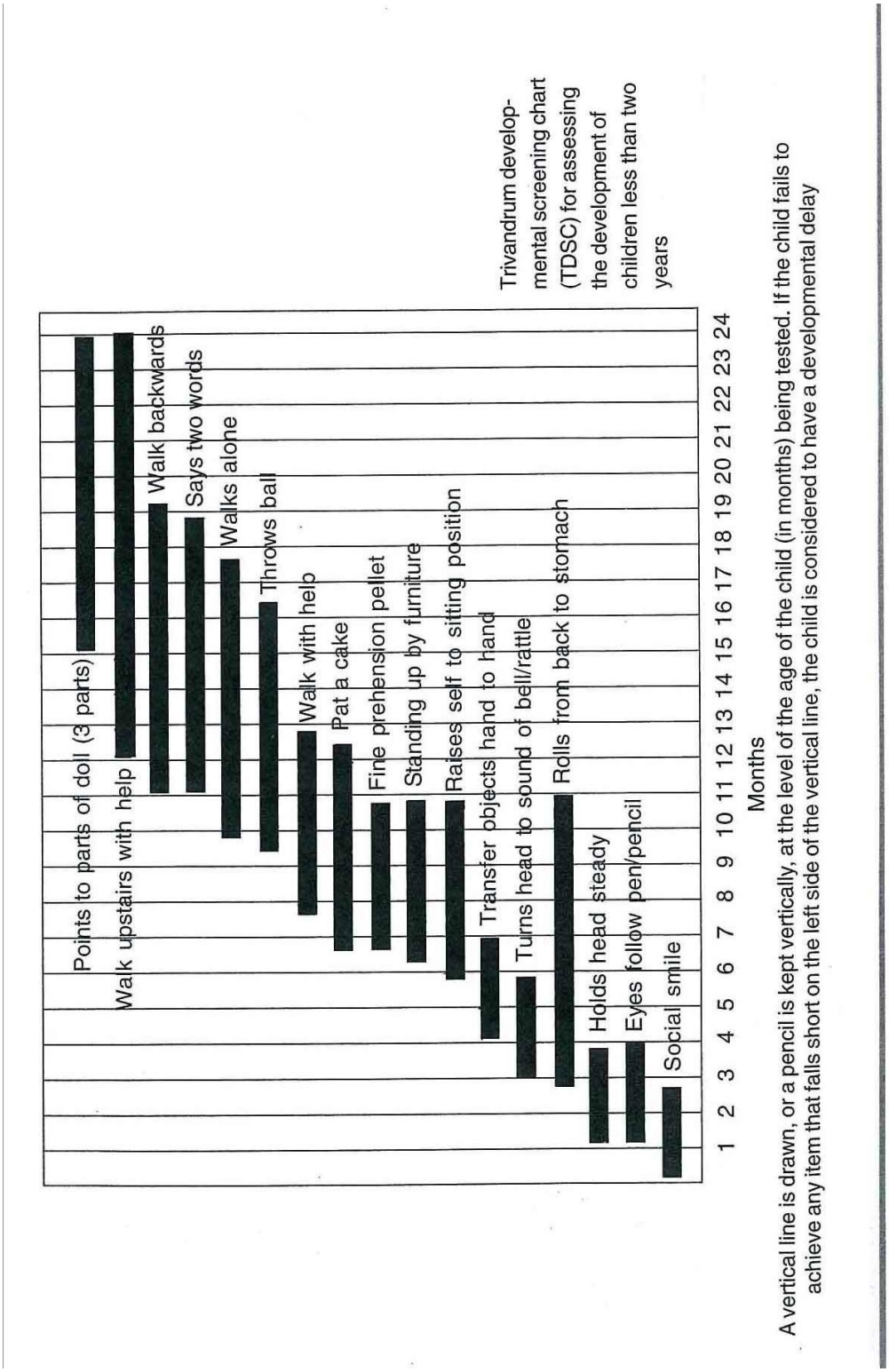
Yours sincerely,

Member Secretary,
Ethics Committee

MEMBER SECRETARY
ETHICAL COMMITTEE,
STANLEY MEDICAL COLLEGE
CHENNAI-600 001.

APPENDIX – 5

TRIVANDRUM DEVELOPMENTAL SCREENING CHART



APPENDIX – 6

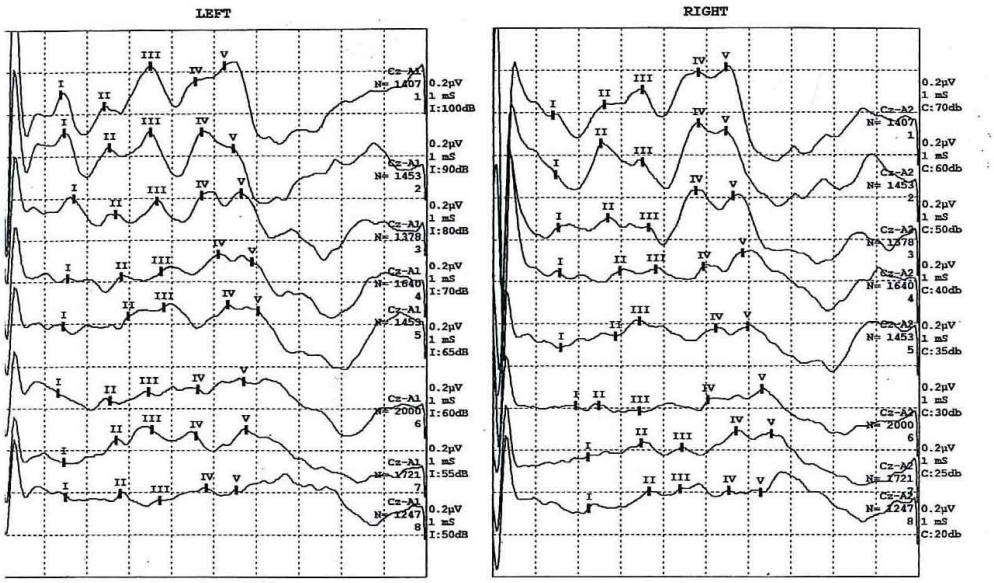
BRAINSTEM EVOKED RESPONSE AUDIOMETRY

Phones 658701-705

Baby.Nasrin | 0 Yrs 0 Mths Female | 0 Cms/0 Kg

sician: Dr.VCM | Ref By: | Date: 28-Jul-2010

AEP RECORD (nHL)



LEFT

Tr	Mont	I (mS)	II (mS)	III (mS)	IV (mS)	V (mS)	I-III (mS)	I-V (mS)	III-V (mS)	I-Ia (μV)	V-Va (μV)	Amp (R)
1	Cz-A1	1.38	2.40	3.50	4.56	5.25	2.13	3.88	1.75	0.23	0.36	1.60
2	Cz-A1	1.46	2.52	3.50	4.71	5.46	2.04	4.00	1.96	0.25	0.17	0.68
3	Cz-A1	1.69	2.67	3.65	4.71	5.65	1.96	3.96	2.00	0.18	0.21	1.13
4	Cz-A1	1.54	2.81	3.75	5.10	5.90	2.21	4.35	2.15	0.08	0.16	1.94
5	Cz-A1	1.44	2.98	3.81	5.33	6.04	2.38	4.60	2.23	0.07	0.14	2.06
6	Cz-A1	1.31	2.54	3.46	4.63	5.71	2.15	4.40	2.25	0.09	0.14	1.66
7	Cz-A1	1.46	2.69	3.54	4.58	5.77	2.08	4.31	2.23	0.03	0.19	5.66
8	Cz-A1	1.50	2.79	3.73	4.83	5.54	2.23	4.04	1.81	0.05	0.07	1.60

RIGHT

Tr	Mont	I (mS)	II (mS)	III (mS)	IV (mS)	V (mS)	I-III (mS)	I-V (mS)	III-V (mS)	I-Ia (μV)	V-Va (μV)	Amp (R)
1	Cz-A2	1.40	2.60	3.50	4.81	5.46	2.10	4.06	1.96	0.16	0.07	0.41
2	Cz-A2	1.46	2.52	3.50	4.81	5.46	2.04	4.00	1.96	0.05	0.25	5.26
3	Cz-A2	1.52	2.69	3.65	4.75	5.63	2.13	4.10	1.98	0.28	0.43	1.52
4	Cz-A2	1.56	2.98	3.81	4.94	5.85	2.25	4.29	2.04	0.30	0.40	1.32
5	Cz-A2	1.58	2.88	3.44	5.23	5.98	1.85	4.40	2.54	0.15	0.25	1.68
6	Cz-A2	1.94	2.48	3.44	5.04	6.31	1.50	4.38	2.88	0.22	0.30	1.37
7	Cz-A2	2.23	3.48	4.44	5.71	6.54	2.21	4.31	2.10	0.24	0.34	1.46
8	Cz-A2	2.25	3.67	4.40	5.54	6.29	2.15	4.04	1.90	0.16	0.24	1.45

Test Comments

NOTE:THE RESULTS MAY BE CLINICALLY CORRELATE

APPENDIX – 7

CONSENT FORM

பெற்றோர் ஒப்புதல் படிவம்

ஆராய்ச்சி நிலையம் : அரசு ஸ்டான்லி மருத்துவமனை,
சென்னை - 600 001.

பங்கு பெறுபவரின் பெயர் :

பங்கு பெறுபவரின் எண் :

பங்கு பெறுவர் இதனை (✓) குறிக்கவும்.

மேலே குறிப்பிட்டுள்ள மருத்துவ ஆய்வின் விவரங்கள் எனக்கு விளக்கப்பட்டது. என்னுடைய சந்தேகங்களை கேட்கவும், அதற்கான தகுந்த விளக்கங்களை பெறவும் வாய்ப்பளிக்கப்பட்டது. ☐

என் குழந்தைக்கு இந்த ஆய்வு செய்ய சம்மதிக்கிறேன். எந்த காரணத்தினாலோ எந்த கட்டத்திலும் எந்த சட்ட சிக்கலுக்கும் உட்படாமல் என் குழந்தையை இந்த ஆய்வில் இருந்து விலகி கொள்ளலாம் என்றும் அறிந்து கொண்டேன். ☐

இந்த ஆய்வு சம்பந்தமாகவோ, இதை சார்ந்த மேலும் ஆய்வு மேற்கொள்ளும் போதும் இந்த ஆய்வில் பங்குபெறும் மருத்துவர் என் குழந்தையுடைய மருத்துவ அறிக்கைகளை பார்ப்பதற்கு என் அனுமதி தேவையில்லை என அறிந்து கொள்கிறேன். என் குழந்தையை ஆய்வில் இருந்து விலகிக் கொண்டாலும் இது பொருந்தும் என அறிகிறேன். ☐

இந்த ஆய்வின் மூலம் கிடைக்கும் தகவல்களையும், பரிசோதனை முடிவுகளையும் மற்றும் சிகிச்சை தொடர்பான தகவல்களையும் மருத்துவர் மேற்கொள்ளும் ஆய்வில் பயன்படுத்திக் கொள்ளவும் அதை பிரசுரிக்கவும் என் முழு மனதுடன் சம்மதிக்கிறேன். ☐

இந்த ஆய்வில் பங்கு கொள்ள ஒப்புக் கொள்கிறேன். எனக்கு கொடுக்கப்பட்ட அறிவுரைகளின்படி நடந்து கொள்வதுடன் இந்த ஆய்வை மேற்கொள்ளும் மருத்துவ அணிக்கு உண்மையுடன் இருப்பேன் என்றும் உறுதியளிக்கிறேன். என் குழந்தையின் உடல் நலம் பாதிக்கப்பட்டாலோ அல்லது எதிர்பாராத வழக்கத்திற்கு மாறான நோய்க்குறி தென்பட்டாலோ உடனே அதை மருத்துவ அணிக்கு தெரிவிப்பேன் என உறுதி அளிக்கிறேன். ☐

இந்த ஆய்வில் என் குழந்தைக்கு இரத்தம், சிறுநீர், எக்ஸரே, காது ஸ்கேன் உட்பட அனைத்து பரிசோதனைகளையும் செய்து கொள்ள நான் முழு மனதுடன் சம்மதிக்கிறேன். ☐

பெற்றோரின் கையொப்பம் ..... இடம் ..... தேதி

கட்டைவிரல் ரேகை

பெற்றோரின் பெயர் மற்றும் விலாசம் .....

ஆய்வாளரின் கையொப்பம் ..... இடம் ..... தேதி

ஆய்வாளரின் பெயர் .....

APPENDIX – 8

ABBREVIATIONS

STB – Serum Total Bilirubin

LBW- Low Birth Weight

BERA- Brainstem Evoked Response Audiometry

ABR- Auditory Brainstem Response

IUGR- Intra Uterine Growth Retardation

TDSC- Trivandrum Developmental Screening Chart

DDST - Denver Developmental Screening Test